

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 August 2002 (22.08.2002)

PCT

(10) International Publication Number
WO 02/064209 A1

(51) International Patent Classification⁷: **A61N 5/06**

(21) International Application Number: **PCT/US01/45851**

(22) International Filing Date:
13 December 2001 (13.12.2001)

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
09/738,523 15 December 2000 (15.12.2000) **US**

(71) Applicant (for all designated States except US): **LUMENIS INC.** [US/US]; 2400 Condensa Street, Santa Clara, CA 95051 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANDERSEN, Dan, E.** [US/US]; 755 Arnold Way, Menlo Park, CA 94025 (US). **BERNSTEIN, Eric, F.** [US/US]; 1321 Grenox Road, Wynnewood, PA 19096 (US).

(74) Agent: **POLLACK, Caleb, J.**; Eitan, Pearl, Latzer & Cohen-Zedek, One Crystal Park, Suite 210, 2011 Crystal Drive, Arlington, NJ 22202-3709 (US).

(81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**

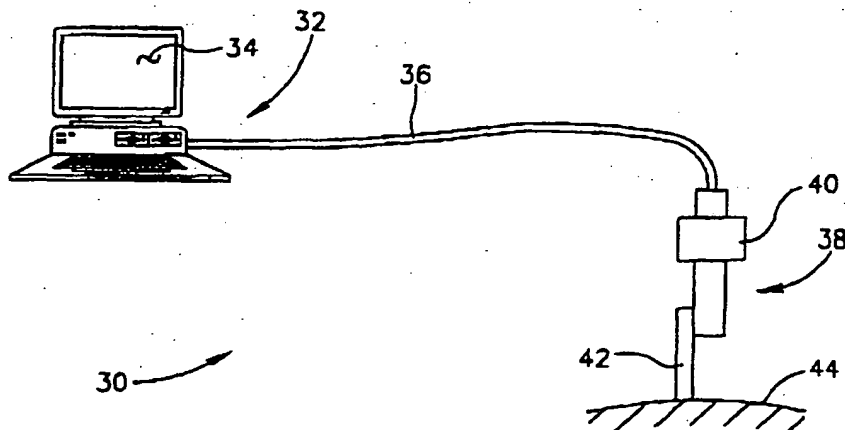
(84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **LASER TREATMENT FOR REDUCING WRINKLES**



(57) Abstract: Skin (10, 12) including wrinkles is irradiated with laser radiation having a wavelength between about 525 and 550 nanometers.

WO 02/064209 A1

LASER TREATMENT FOR REDUCING WRINKLES

The present invention relates in general to laser treatment of dermatological imperfections. The invention relates in particular to non-ablative laser treatment for reducing wrinkles.

DISCUSSION OF BACKGROUND ART

Effective aesthetic treatment of wrinkles has hitherto involved primarily the removal of tissue and subsequent wound healing to improve their appearance. Chemical peels, dermabrasion, and ablative laser skin resurfacing are used routinely for this purpose. However, all of these methods leave open wounds that must subsequently heal. There is
10 need for a laser treatment method for reducing wrinkles that does not leave such open wounds.

SUMMARY OF THE INVENTION

The present invention is directed to a method for treating wrinkles. In one aspect, the method of the present invention comprises irradiating the skin to be treated with light
15 (electromagnetic radiation) having a wavelength selected such that it is preferentially absorbed in a dermal region of the skin including a melanocyte layer of the epidermis and a region of superficial vasculature immediately below the melanocyte layer. The light is delivered at a fluence sufficient that the preferential absorption thereof stimulates a wound healing (regenerative) response in the dermal region without causing a wound. The wound
20 healing response promotes growth of dermal extracellular matrix (ECM) in the upper dermal region. The growth of dermal ECM reduces the depth of the wrinkles.

Preferably, the light has a wavelength between about 525 and 550 nanometers (nm). The light may be delivered in the form of pulses thereof or as a continuous beam swept or scanned over an area of skin being treated.

In experimental treatments in accordance with the present invention, pulsed
5 electromagnetic radiation having a wavelength of 532 nm, delivered by a frequency-doubled Nd:YAG laser was arranged to deliver a spot having a diameter of about 3 millimeters (mm). The pulse duration was about 2.0 milliseconds (ms). An average fluence of 5.5 Joules per square centimeter (J/cm^2) was used in repeated treatments to treat eleven volunteer patients having facial wrinkles. There was on average a 52%
10 improvement in the appearance of the wrinkles, as judged by the patients themselves.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and constitute a part of the specification, schematically illustrate a preferred embodiment of the present invention and, together with the general description above and the detailed description of the preferred
15 embodiment given below, serve to explain the principles of the invention.

FIG. 1 schematically illustrates a section of human tissue including layers and vasculature thereof.

FIG. 2 is a graph schematically illustrating absorptivity of hemoglobin and melanin as a function of wavelength in a wavelength region of the visible electromagnetic spectrum
20 between 500 nanometers and 600 nanometers.

FIG. 3 schematically illustrates laser apparatus used for experimental treatment of wrinkles in accordance with the method of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The method of the present invention relies on using laser radiation to stimulate the skin's regenerative or wound healing responses. The laser radiation wavelength and the laser radiation fluence are selected such that the wound healing responses are stimulated without actually inflicting a wound. The wound healing responses promote growth or
5 production of dermal ECM. The term "wound" here is meant to define an open wound, blister or any other effect that would be manifest in, or lead to, a discontinuity in the structure of the tissue.

The biology of wound healing is a very complex process. Cytokines released by the vascular endothelial cells and epidermal keratinocytes are responsible for initiating the
10 increased production of ECM. These elements lie in the uppermost regions of the skin. This ECM production process takes place in a series of interrelated steps via the resident cells of the dermis. By selecting a wavelength of laser radiation in a range between about 525 and 550 nm, there is an optimal stimulation of both keratinocytes and vascular endothelial cells, which causes the wound healing response to be concentrated close to
15 these upper regions of the skin, and accordingly close to the location of imperfections being treated.

The dermis is composed of cellular and extracellular constituents that interact with one another to form a highly ordered yet quite dynamic structure. Other than water, the major components of the ECM are collagen, elastic fibers, fibronectin,
20 glycosaminoglycans, and proteoglycans. The stimulated growth of dermal ECM "bulks up" the dermal tissue. This makes the depressions or "folds" of wrinkles shallower and less apparent, if not eliminating them altogether.

The superficial vascular endothelium and the epidermal keratinocytes are stimulated by heating them with light that is well absorbed by components within both structures.

This requires that the light be optimally absorbed in both melanin and in hemoglobin of the superficial vasculature.

FIG. 1 schematically illustrates a section of human skin including a region 10 generally defined as the epidermis and a region 12 generally defined as the dermis. The epidermis 10 includes an outer layer (stratum corneum) 14, and a lower (melanocyte) layer 16 including melanin pigment. Some keratinocytes are heavily pigmented and contain melanosomes that feed melanin to surrounding cells. These cells are called melanocytes. The epidermis is made up primarily of keratinocytes.

In the papillary or upper dermis 12, vasculature 18 has a superficial portion thereof comprising a plurality of capillary loops 20. In the method of the present invention, absorption by melanin in melanocyte layer 16 and hemoglobin in capillary loops 20 of vasculature 18 preferentially heats a shallow region 20 immediately below layer 16, thereby heating the layer by conduction and providing the desired wound healing stimulus. It is believed, without being limited to a particular theory, that heating of endothelial cells in the walls of vessels of vasculature 18, in particular of the capillary loops 20 close to the epidermis 10, induces the secretion of cytokines that stimulate cells of the dermis 12 to produce the ECM.

FIG. 2 graphically, schematically illustrates absorptivity of blood (curve A) and melanin (curve B) as a function of wavelength in a wavelength region between 500 nm and 600 nm in the visible electromagnetic spectrum. In the preferred wavelength region of 525 to 550 nanometers, absorptivity in hemoglobin is at or near a peak while absorption in melanin is also at a high level. The high melanosome absorptivity helps in maintaining the desired heating effect at a superficial level in the skin being treated. By way of contrast, in the "yellow" wavelength region around 580 nm where dye lasers emit, melanosome

absorptivity is significantly less than at 525 nm and approaches equality with hemoglobin absorptivity. This is one reason why dye lasers are preferred in prior-art treatment of vascular disorders and the like. In such treatments, absorption of radiation by melanin could cause undesirable side effects such as blistering of skin as well as preventing
9 penetration of the radiation to the lower lying vasculature where it is needed.

In the inventive wrinkle treatment method, electromagnetic radiation (light) preferably having a wavelength between about 525 and 550 nm, and having an appropriate pulse duration and intensity, is used to provide a selective, localized temperature increase in the superficial vasculature 20 and, intentionally and therapeutically, in melanocyte layer 16.
10 The temperature rise should be sufficient to stimulate the release of cytokines and other growth factors without appreciably damaging any of the structures of the skin. Preferably this temperature is less than about 70°C, but must, of course, be higher than normal body temperature. It is believed that at wavelengths increasingly shorter than 525 nm, as absorption becomes increasingly, proportionately higher in melanin than in hemoglobin,
15 sufficient heating of the target region cannot be obtained without overtreating the melanocyte layer and causing blistering. At wavelengths increasingly longer than 550 nm, decreasing melanin absorption will allow penetration of radiation to depths in the vasculature at which it is less therapeutically effective, if at all.

The treatment radiation is preferably delivered by a laser. One suitable laser for
20 providing radiation in the inventive treatment of wrinkles is a frequency doubled Nd:YAG laser. Such a laser operates most efficiently by generating 1064 nm fundamental radiation and converting this radiation to 532 nm radiation by intracavity frequency doubling.

Referring now to FIG. 3, laser apparatus 30 used for experimental treatments in accordance with the present invention includes a Coherent® "VersaPulseV™"

intracavity-frequency-doubled Nd:YAG laser 32 including a touch screen control display 34 for controlling operating parameters of the laser. Laser 32 delivers 532 nm radiation via a fiber-optic cable 36 to a handpiece 38. Handpiece 38 includes optics (not shown) that allow delivery of the 532 nm laser radiation focussed in a range of spot sizes. Spot sizes are selectively adjustable by rotating a control ring 40. A stand-off probe 42 attached to handpiece 38 contacts tissue 44 being treated to ensure that radiation is always delivered in the same spot size as the handpiece is moved to different locations on tissue 44. It is also possible to employ a handpiece that delivers a collimated beam. This allows for a range of variation of working distance while still maintaining a selected beam size.

10 In experimental treatments in accordance with the present invention, laser 32 was arranged to deliver a spot having a diameter of about 3 mm. The pulse duration was about 2.0 ms. An average fluence of 5.5 J/cm² was used to treat facial wrinkles of volunteer patients. A total of eleven volunteer patients were treated.

15 Wrinkles were treated by applying single pulses at adjacent locations over the area without overlapping pulses. There was a high degree of patient satisfaction with the improvement of their appearance after an average of three treatments (one treatment about every three to five weeks). There was on average about a 52% improvement in wrinkles, the judgement of improvement being made by the patients themselves.

20 In establishing a suitable fluence for treatment for each patient, test pulses were delivered to a selected test area of that patient's skin, in a range of increasing fluences, until a fluence level was reached that produced observable, but mild erythema. Each test pulse was fired on a different portion of the patient's skin. It was found that fluences higher than 12 J/cm² at a pulse length of 2 ms generally caused immediate blistering, even on light-skinned patients. Accordingly a fluence less than about 10 J/cm² in a pulse having a

duration of about 2 ms or somewhat less is preferred. It should be noted here that this simple inflammation does not constitute a wound as that term is defined herein. Under no circumstances should the treatment parameters be sufficient to cause coagulation of blood in the vasculature.

5 Inflammation is a very specific process and is not synonymous with irritation. It is emphasized, however, that it is not necessarily the inflammation in itself that is responsible for the dermal ECM deposition and corresponding improvements of the inventive treatment. Rather, it is believed that it is the directed inflammatory process of the present invention that promotes the ECM growth, whether or not inflammation is clinically evident.
10 Numerous inflammatory skin conditions, such as vasculitis, Sweet's syndrome and insect bites, occur without deposition of dermal ECM.

 The experimental treatments were performed without resort to any skin cooling mechanisms such as contact cooling, cryogen spray cooling or the application of cooling gels to areas being treated. It is possible, however, that the method of the present invention
15 may be made part of an integrated approach to the treatment of wrinkles by combining the above-described radiation therapy with application of agents such as alpha-hydroxy acids, retinoids and growth factors that can positively impact the healing response.

 It should be noted here that while the above-described treatments were conducted using the 532 nm wavelength of a frequency-doubled Nd:YAG, this particular wavelength
20 should not be construed as limiting the invention. By way of example, using an appropriately wavelength selective resonator, a frequency doubled Nd:YAG laser can be arranged to deliver other wavelengths in the region between about 525 nm and 555 nm. These other wavelengths are about 531 nm, about 537 nm, and about 539 nm, which can be produced by frequency doubling fundamental radiation at respectively about 1061 nm,

about 1073 nm, and about 1078 nm, the term "about" here meaning that the wavelengths are stated as rounded to the nearest nanometer. 532 nm radiation may also be generated by a frequency-doubled Nd:YVO₄ laser. The use of any other laser providing radiation in the preferred, 525 to 550 nm, range is not precluded in the present invention, nor is the use of
5 any source of non-coherent light delivering radiation in this preferred wavelength range.

It should also be noted that while single pulse delivery of radiation in experimental treatments is described, it is also possible to use continuous wave (CW) radiation and scan the radiation over tissue being treated. Scan speed (accordingly the dwell time of a beam in a particular area) can be selected, consistent with the beam-size and power in the CW
10 beam, such that the dwell time of radiation at a point being treated (due to the time taken for a beam of finite size to pass that point) delivers the appropriate fluence as indicated above.

The present invention is described above in terms of a preferred and other embodiments. The invention is not limited, however, by the embodiments described and
15 depicted herein. Rather, the invention is limited only by the claims appended hereto.

CLAIMS

What is claimed is:

1. A method for treating wrinkles in human skin, comprising:
irradiating the skin with light having a wavelength between about 525
5 nanometers and 550 nanometers at a fluence level sufficient to promote a
wound healing response in the skin but insufficient to cause a wound.
2. The method of claim 1, wherein said wavelength is about 532 nanometers.
3. The method of claim 1, wherein said fluence is less than about 10 J/cm².
4. The method of claim 1, wherein said light is delivered in the form of one or more
10 pulses.
5. The method of claim 4, wherein said one or more pulses each has a duration of
about 2 milliseconds or less.
6. The method of claim 1, wherein said light is delivered as CW radiation and is
scanned over an area of skin being treated.
- 15 7. The method of claim 1, wherein said light is coherent light delivered by a laser.
8. The method of claim 1, wherein said light is incoherent light.
9. The method of claim 1, wherein said light is absorbed preferentially in a region of
skin including a melanocyte layer of the epidermis and a region of superficial
vasculature immediately below said melanocyte layer, thereby heating said region of
20 skin to a temperature higher than normal body temperature but less than about 70°C, said
heating promoting said wound healing response.
10. A method for treating wrinkles in human skin, comprising:

irradiating the skin with light having a wavelength between about 525 nanometers and 550 nanometers such that a region of the skin including a melanocyte layer of the epidermis and a region of superficial vasculature immediately below said melanocyte layer are heated to a temperature higher than normal body temperature but less than about 70°C, said heating stimulating the production of dermal extracellular matrix in said region of the skin, said dermal extracellular matrix production reducing the depth of said wrinkles.

11. The method of claim 9, wherein said wavelength is about 532 nanometers.
- 10 12. The method of claim 9, wherein said fluence is less than about 10 J/cm².
13. The method of claim 9, wherein said light is delivered in the form of one or more individual pulses.
14. The method of claim 13, wherein said one or more pulses each has a duration of about 2 milliseconds or less.
- 15 15. The method of claim 9, wherein said light is delivered as CW radiation and is scanned over an area of skin being treated.
16. The method of claim 9, wherein said light is coherent light delivered by a laser.
17. The method of claim 9, wherein said light is incoherent light.
18. A method for treating wrinkles in human skin, comprising:
20 irradiating the skin with light having a wavelength selected such that it is preferentially absorbed in a region of the skin including a melanocyte layer of the epidermis and a region of superficial vasculature below said melanocyte layer, said light being delivered at a fluence sufficient that said

preferential absorption thereof stimulates a wound healing response in said region of the skin without causing a wound, said wound healing response promoting growth of dermal extracellular matrix in said region of the skin, thereby reducing the depth of said wrinkles.

- 5 19. The method of claim 18, wherein preferential absorption heats said dermal region to a temperature higher than normal body temperature but less than about 70°C, said heating stimulating said wound healing response.

1/2

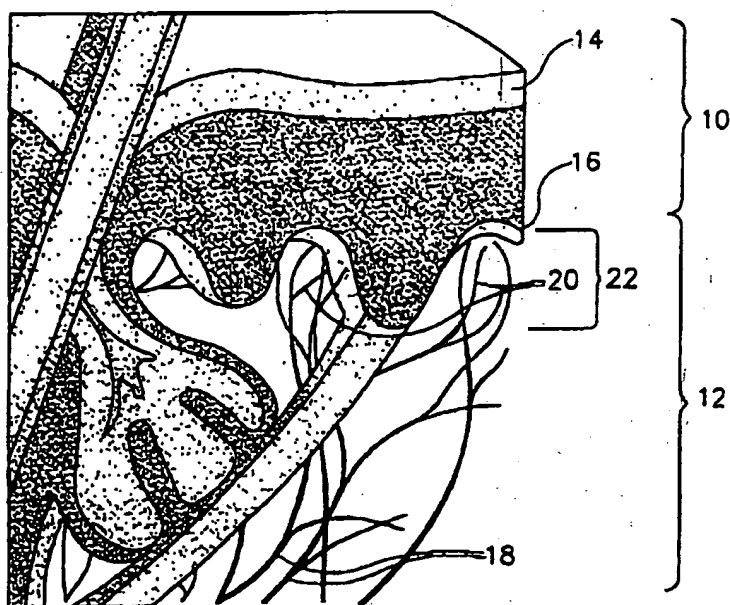


FIG.1

2/2

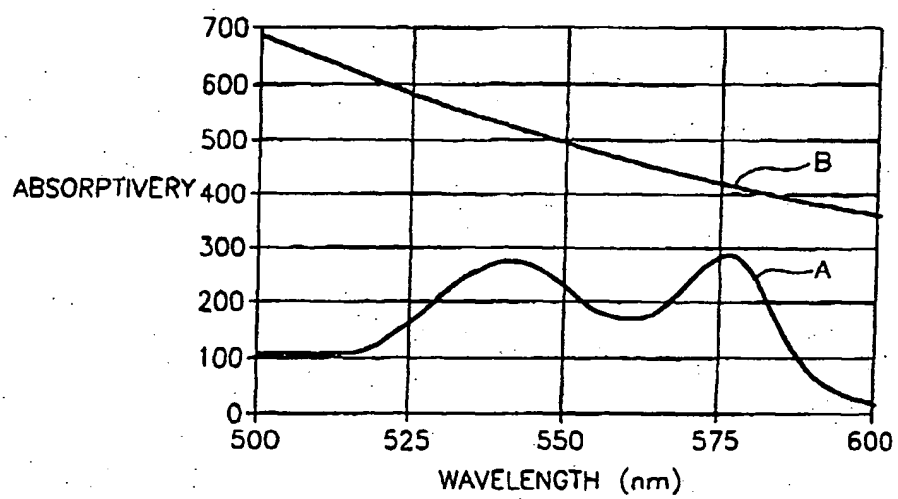


FIG.2

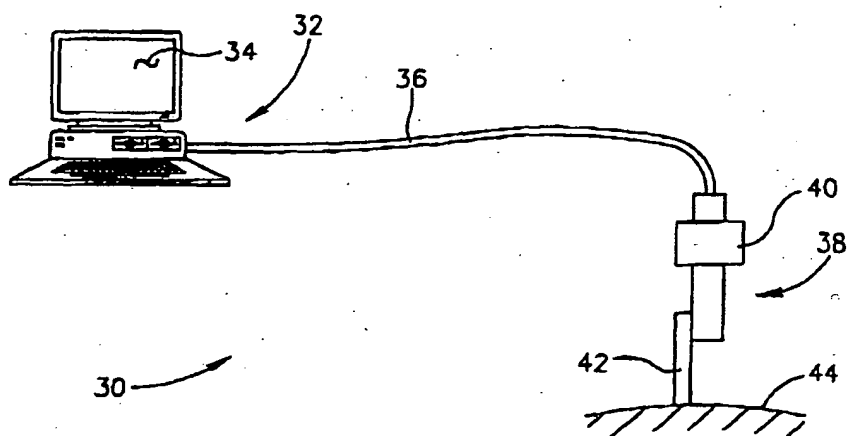


FIG.3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/45851

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61N 5/08

US CL : 606/9; 607/88, 89, 90, 91

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 606/9; 607/88, 89, 90, 91

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,387,089 B1 (KREINDEL et al) 14 May 2002, entire patent.	1-19
Y	US 5,312,395 A (TAN et al) 17 May 1994, see entire patent.	1-19
Y	US 5,810,801 A (ANDERSON et al) 22 September 1998, see entire patent.	1-19
Y	US 6,210,426 B1 (CHO et al) 03 April 2001, see entire patent.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 JUNE 2002

Date of mailing of the international search report

11 JUL 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

GEORGE L. WALTON

Telephone No. (703) 308-2596